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(54) Title: GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

(57) Abstract: The present invention provides gene expression systems useful for detecting agonists of Toll-like receptors. The gene expression systems include a nucleic acid sequence encoding a Toll-like receptor and a second nucleic acid sequence that encodes a reporter operably linked to an expression control sequence. The recombinant cell lines include a gene expression system according to the present invention.

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GENE EXPRESSION SYSTEMS AND RECOMBINANT CELL LINES

Background of the Invention

Cells of the immune system secrete a diverse set of compounds including cytokines, chemokines, co-stimulatory markers, and defensins in response to an immunological challenge.

Certain compounds known as immune response modifiers ("IRMs") possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by, e.g., inducing the production and secretion of certain cytokines while inhibiting production and secretion of other cytokines. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,245,776; 6,039,969; 6,083,969; 6,245,776; 6,331,539; and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,50 and 6,028,076), small heterocyclic compounds (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116; 6,339,068; and 6,406,705. Other IRM nucleotide sequences lack CpG and are described, for example, in International Patent Publication No. WO 00/75304.

Some of these IRMs induce cellular responses (e.g., the production and/or secretion of cytokines, chemokines, etc.) through one or more Toll-like receptors (TLRs). For example, certain small organic molecule IRMs are agonists of one or more of TLR-1, TLR-2, TLR-4, TLR-6, TLR-7, and TLR-8. Additionally, CpG has been reported to act through TLR 9.

In certain cells of the immune system, TLR activation can be associated with activation of the transcription factor NF-κB. NF-κB activation is associated with certain cellular responses to an immunological challenge, such as the production and secretion of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. IRM induction of such cellular responses can be demonstrated by measuring activation of the transcription factor NF-κB in response to exposing a cell to an IRM compound (See, e.g., Chuang *et al.*, *Journ. of Leuk. Biol.*, vol. 71, pp. 538-544 (2002), and Hemmi *et al.*, *Nature Immunology*, vol. 3(2), pp. 196-200 (2002)). Thus, NF-κB activation can be used as a reporter of TLR activation. However, the extent of NF-κB activation does not necessarily correlate with the extent of the downstream cellular response. This is so because the downstream cellular response may be modulated by one or more additional factors.

Summary of the Invention

The present invention provides an expression system that includes a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter. In some embodiments, the first nucleic acid sequence and the second nucleic acid sequence are included on a single vector. In other embodiments, the first nucleic acid sequence and the second nucleic acid sequence are located on separate vectors.

In another aspect, the present invention provides a recombinant cell line that includes a host cell transfected with an expression system. In some embodiments, the expression system is contained within a single vector. In other embodiments, the expression system is contained among two or more vectors so that the host cell is co-transfected with all of the vectors of the expression system to obtain the recombinant cell line. In one embodiment, the host cell is a Namalwa cell.

In another aspect, the present invention provides a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

In yet another aspect, the present invention provides pharmaceutical compositions including a TLR agonist identified using either an expression system or a recombinant cell line according to the present invention.

Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, and appended claims. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

Detailed Description of Illustrative Embodiments of the Invention

The present invention provides gene expression systems and recombinant cell lines that may be useful for detecting TLR activation based on detecting induction of a downstream cellular response to TLR activation (e.g., production or secretion of one or more immune system compounds such as cytokines or co-stimulatory markers) rather than NF-κB activation. In some cases, the cellular response may be mediated by NF-κB, but in other cases the cellular response may be NF-κB-independent. Thus, the present invention provides gene expression systems and recombinant cell lines that may be useful for detecting a broader range of TLR activation than is possible by monitoring NF-κB activation. This may provide an ability to identify certain TLR agonists that would not be detected using an assay based on NF-κB activation. The gene expression systems and recombinant cell lines of the present invention also may provide a more relevant indication of the quantitative character of a particular cellular response to TLR activation by a particular TLR agonist.

In some cases, a gene expression system or recombinant cell line according to the present invention may be useful for detecting TLR activation that is not accompanied by NF-κB activation. Accordingly, the gene expression system and recombinant cell line may be employed to identify TLR agonists that do not necessarily also activate NF-κB. Such TLR agonists may be useful for treatment or prevention of certain conditions in which the production and secretion of pro-inflammatory cytokines such as those induced by NF-κB activation may be undesirable.

For purposes of this invention, the following terms shall have the meanings set forth.

"Activation" refers to modifying the indicated protein so that the protein provides a biological function. For example, TLR activation refers to modifying a TLR - for example, a conformational modification such as in response to exposure of the TLR to an agonist - so that the TLR is capable of inducing the production and secretion of certain cytokines.

"Agonist" refers to a compound that can combine with a receptor (e.g., a TLR) to produce a cellular response. An agonist may be a ligand that directly binds to the receptor. Alternatively, an agonist may combine with a receptor indirectly by, e.g., (a) forming a complex with another molecule that directly binds to the receptor, or (b) otherwise results in the modification of another compound so that the other compound directly binds to the receptor. An agonist may be referred to as an agonist of a particular TLR (e.g., a TLR6 agonist).

"Amino acid sequence" refers to a particular ordered sequence of amino acids, whether naturally occurring or engineered.

"Co-transfect" and variations thereof refer to transfecting a host cell with more than one vector. A host cell may be co-transfected by transfecting with two or more vectors one at a time or in any convenient combination of vectors, including simultaneous transfection with all vectors.

"Express" and variations thereof refer to the ability of a cell to transcribe a structural gene to mRNA, then translate the mRNA to synthesize a protein that provides a detectable biological or biochemical function. "Expressible" refers to the ability of a particular nucleic acid sequence to be expressed by a cell that contains the nucleic acid sequence.

"Immune system compound" refers to any compound that is produced or secreted by cells of the immune system in response to an immunological challenge. Immune system compounds include but are not limited to cytokines, chemokines, co-stimulatory markers, and defensins.

"IRM compound" refers to a compound that alters the level of one or more immune system compounds when administered to an IRM-responsive cell. Representative IRM compounds include the small organic molecules, purine derivatives, small heterocyclic compounds, amide derivatives, and oligonucleotide sequences described above.

"Nucleic acid sequence" refers generally to a region of DNA that has a definable function such as (a) encoding a peptide, polypeptide, or protein or (b) controlling expression of a nucleic acid sequence that encodes a peptide, polypeptide, or protein. For example, a nucleic acid sequence that encodes TLR6 refers generically to any sequence of nucleotides that encodes a TLR6 protein, without regard to (a) the species source of the nucleic acid sequence, (b) specific nucleotide sequence variants, or (c) whether such nucleotide sequence variants are naturally occurring or engineered.

"Nucleotide sequence" refers to a particular ordered sequence of nucleotide bases, whether naturally occurring or engineered.

It has been found that induction of certain secreted proteins or polypeptides can be useful as reporters of TLR activation. For example, IFN-α is a cytokine secreted by such immune system cells as T lymphocytes, macrophages, plasmacytoid monocytes, dendritic cells, and natural killer cells. IFN-α is involved in regulating a host's innate and adaptive immune responses to an immunological challenge, perhaps by providing a link between the two responses [Brassard *et al., Journal of Leukocyte Biology* 71: 565-581 (2002)]. The innate immune response can include the cell-mediated response of natural killer (NK) cells to a non-self (e.g., neoplastic) or foreign (e.g., viral) antigen. IFN-α also may indirectly regulate the balance between Th1 and Th2 cell populations and, therefore, the innate and adaptive immune responses. Moreover, induction of IFN-α is independent of NF-κB activation.

Additionally, the production and secretion of NF-κB-dependent cytokines can be useful as reporters of cellular responses resulting from immunological challenge. Detection and measurement of such cytokines may provide comparative qualitative data regarding a cell's response to immunological challenge that is more relevant to an investigator than NF-κB activation data.

Thus, in certain embodiments, the present invention relates to recombinant cell lines and gene expression systems designed to assist detecting induction of immune system compounds and identification of compounds that induce expression of immune system compounds through TLRs.

Parts of the following description are provided in the context of IFN-α induction and detection. However, many of the features of the embodiments described below also may be realized using expression systems and recombinant cell lines designed to specifically detect or induce other immune system compounds. Thus, expression systems and recombinant cell lines designed to specifically detect or induce immune system compounds other than IFN-α are explicitly included in the scope of the present invention.

The present invention provides a recombinant cell line capable of inducing gene expression from an expression control sequence of a gene that encodes an immune system compound (e.g., IFN-α) in response to TLR activation. In some embodiments, for example, cells of the recombinant cell line, when exposed to a TLR agonist, can induce expression from an IFN-α promoter to a greater extent than cells of the corresponding untransfected cell line. Cells of the untransfected cell lines may substantially lack a functional level of TLR expression (i.e., untransfected cells may not detectably induce expression from the IFN-α promoter in response to exposure to a TLR agonist). Alternatively, cells of the untransfected cell line may exhibit a baseline level of background TLR function, but the baseline level is less than the level of TLR function observed in cells of the corresponding recombinant (i.e., transfected) cell line.

Cells of the recombinant cell lines include a first nucleic acid sequence that encodes a TLR operably linked to an expression control sequence. The cells also include a second nucleic acid sequence that encodes a reporter capable of generating a detectable signal when it is expressed in the recombinant cell under conditions suitable for generating the detectable signal. The reporter is linked to a second expression control sequence that is capable of being induced by activation of the TLR encoded by the first nucleic acid sequence.

The TLR encoded by the first nucleic acid sequence may be any TLR. Ten different human TLRs have been identified, cloned, and sequenced. TLRs also are known to exist in other mammals including, for example, mice and chimpanzees. The nucleotide sequences of the ten human TLRs and many non-human TLRs are known, have been published, and are readily accessible from various sequence databases including GenBank. The first nucleic acid sequence may include the nucleotide sequence of any one of the TLRs, whether human or non-human. In one embodiment, the TLR is human TLR6; in another embodiment, the TLR is human TLR7. Alternatively, the first nucleic acid may encode any one of the ten human TLRs, any non-human TLR, or any combination of two or more TLRs that may be desirable for a particular construct.

The first nucleic acid sequence can include a nucleotide sequence that differs from a specific published nucleotide sequence for the TLR encoded by the first nucleic acid sequence. For example, the first nucleic acid sequence can contain one or more substitutions (compared to a published TLR nucleotide sequence) that do not alter the amino acid sequence of the TLR protein expressed from the first nucleic acid sequence. Such a substitution may be termed a degenerate substitution. Nucleotide sequences containing one or more degenerate substitutions compared to a known TLR nucleotide sequence are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

As another example, certain nucleotide substitutions may alter the amino acid sequence of the TLR protein. For certain amino acid substitutions, however, the chemical properties of the protein having the altered amino acid sequence are similar to the chemical properties of the protein having the native amino acid sequence. Amino acids may be divided into four groups based on the chemical characteristics of the amino acid side groups: neutral, non-polar amino acids include glycine, alanine, valine, isoleucine, leucine, phenylalanine, proline, and methionine; neutral, polar amino acids include serine, threonine, tyrosine, tryptophan, asparagine, glutamine, and cysteine; acidic amino acids include aspartic acid and glutamic acid; and basic amino acids include lysine, arginine, and histidine. Substitution of one amino acid for another amino acid within the same group may have little or no functional effect on the resulting protein because of the similarity of the chemical characteristics of the amino acids involved in the substitution. Such amino acid substitutions may be termed a conservative amino acid substitution. Nucleotide sequences that, when compared to a known TLR nucleotide sequence, generate one or more conservative amino acid substitutions are explicitly included within the scope of nucleotide sequences suitable for use within the first nucleic acid sequence.

The nucleic acid that encodes a TLR may be cloned into an expression vector so that it is under the expression control of its own promoter, a homologous TLR promoter, or any heterologous promoter inducible in an appropriate host cell. For example, in certain embodiments, the TLR6 structural gene may be cloned into the commercially available mammalian expression vector pCI-neo. In this case, the TLR6 structural gene may be cloned into the vector's cloning region using the NheI and MluI restrictions sites. In such an embodiment, after transfection of the vector into a mammalian cell, the TLR6 structural gene is under the transcriptional control of the vector's CMV enhancer/promoter region.

The second nucleic acid sequence encodes a reporter that is capable of generating a detectable signal when expressed in a host cell under conditions appropriate for generating the desired detectable signal. A wide variety of suitable reporter systems are known. For example, luciferase gene expression may generate a detectable luminescent signal under appropriate conditions. As another example, β-galactosidase expression can generate a detectable color change under appropriate conditions. As yet another example, production and secretion of an immune system compound may be detected by an enzyme-linked immunosorbent assay (ELISA). These and other reporter systems are known and assays for generating the detectable signals are commercially available.

The second nucleic acid sequence is operably linked to a second expression control sequence that includes a promoter sequence selected to be inducible by activation of the TLR encoded by the first nucleic acid sequence. Thus, expression and activation of the TLR encoded by the first nucleic acid sequence will induce gene expression from the second expression control sequence, thereby causing expression of the reporter, which may be detected by performing an assay designed to detect expression of the reporter. The second expression control sequence may include any suitable nucleotide sequence that can induce expression (e.g., a promoter) of a structural gene upon activation of the TLR encoded by the first nucleic acid sequence. Nucleotide sequences suitable for use as second expression control sequences include promoter sequences of TLR-inducible genes including but not limited to genes encoding cytokines, chemokines, co-stimulatory markers, and defensins. In certain embodiments, the second expression control sequence can include an IFN-α1 promoter. When the reporter system being employed to detect TLR activation includes detecting production and secretion of an immune system compound with an appropriate ELISA assay, the second expression control sequence may include the promoter of the gene encoding the immune system compounds being expressed and detected as the reporter. However, in certain embodiments, it may be desirable to express the immune system compound from a heterologous promoter.

The first nucleic acid sequence and the second nucleic acid sequence may be contained within a single vector. Alternatively, the first nucleic acid sequence and the second nucleic acid sequence may be on separate vectors and co-transfected into a suitable host cell. In certain embodiments, for example, the first nucleic acid sequence may be cloned into the pCI-neo vector as described above, while the second nucleic acid sequence can be cloned into a reporter vector. One example of a commercially available reporter vector is the pGL3-Enhancer vector, which includes a luciferase reporter gene downstream of a cloning site for cloning a promoter sequence of interest. In some embodiments, the promoter of a TLR-inducible immune system compound may be cloned into the pGL3-Enhancer cloning site. In one such embodiment, the IFN-α promoter may be cloned into the pGL3-Enhancer cloning site.

Suitable host cells include any transfectable cells capable of expressing exogenous mammalian genes. In some embodiments, the host cells may be mammalian cells such as human cells or mouse cells. For example, suitable host cells include human cells or descendants of a human cell including but not limited to Namalwa cells or HEK293 cells. Alternatively, the host cells may be mouse cells or descendants of a mouse cell including but not limited to RAW 264.7 cells.

In one embodiment, the host cells include Namalwa cells. Namalwa cells have certain characteristics that may be particularly desirable for certain embodiments of the present invention. For example, Namalwa cells can include an expressible chromosomal IFN-α gene locus. Thus, upon appropriate stimulation (e.g., viral infection), Namalwa cells can be induced to produce and secrete IFN-α from the chromosomal IFN-α gene locus. However, Namalwa cells do not naturally express certain TLRs (e.g., TLR6, TLR7, or TLR9). Certain agonists of such TLRs have been shown to induce IFN-α expression in other cell types (e.g., PMBCs), but may not induce IFN-α expression in Namalwa cells unless a functional level of TLR expression is provided.

Namalwa cells transfected with an expression system according to the present invention may be capable of expressing a functional level of the TLR provided by the expression system. Thus, Namalwa cells transfected with an expression system according to certain embodiments of the present invention may inducibly express IFN-α as a result of activating the cloned TLR (e.g., by exposure of the transfected Namalwa cells to an agonist). Thus, certain transfected cell lines of the present invention provide an ability to detect a TLR agonist by detecting TLR-mediated IFN-α expression by Namalwa cells. Such IFN-α expression may occur from the chromosomal IFN-α gene or from an IFN-α promoter cloned into the reporter vector.

Namalwa cells transfected with an expression system according to certain embodiments of the present invention can provide alternative means of detecting TLR expression. First, transfected Namalwa cells may generate a detectable signal as a result of expressing the reporter from the second expression control sequence, which may or may not include an IFN-α promoter (see Table 2). Second, transfected Namalwa cells may produce and secrete IFN-α from the chromosomal IFN-α gene locus. A transfected Namalwa cell line according to the present invention may be used to screen compounds in order to identify those compounds that induce TLR expression, i.e., TLR agonists.

Therefore, the present invention also provides TLR agonist compounds identified using an expression system or a recombinant cell line according to certain embodiments of the present invention. As described above, the expression systems and recombinant cell lines may provide the ability to identify TLR activation that may not be detectable using previously known TLR activation assays. A compound that induces TLR activity detectable by using a gene expression system or a recombinant cell line according to the present invention may be considered a TLR agonist. Such TLR agonists may include chemical structures similar in certain respects to the chemical structures of known IRM compounds. Alternatively, a gene expression system or a recombinant cell line according to the present invention may provide a tool for the screening (e.g., high throughput screening) chemically diverse compounds that may lead to the discovery of new TLR agonists, some of which may contain new chemical core structures capable of activating TLRs.

The present invention also provides pharmaceutical compositions containing a TLR agonist identified using an expression system or a recombinant cell line according to the present invention, or a pharmaceutically acceptable salt thereof, in an amount effective for inducing a TLR-mediated cellular response.

Examples

The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

Construction of vectors

The vector pIFN-α1-luc was constructed by inserting BglII sites at both ends of the human IFN-α1 promoter (SEQ ID NO:21). The BglII sites were inserted into the IFN-α1 promoter and the sequence was amplified using the primer pair of SEQ ID NO:22 and SEQ ID NO:23. The amplified IFN-α1 promoter was cloned into the pGL3-Enhancing vector (Promega Corp., Madison, WI) at its BglII site.

The vector pCI-TLR6 was constructed by inserting SEQ ID NO:11 (GenBank Accession No. NM 006068), which includes the human TLR6 coding sequence, into the pCI-neo mammalian expression vector (Promega Corp.) at the vector's NheI and MluI restriction sites.

Transfections

Unless otherwise indicated, all incubations were performed at 37°C with 5% CO_2 at 98% humidity.

Culture medium was prepared from complete RPMI 1640 medium (BioSource International, Inc., Camarillo, CA). Fetal bovine serum (Atlas Biologicals, Inc., Ft. Collins, CO) was added to a final concentration of 7.5% (vol/vol); L-glutamine (BioSource International, Inc.) was added to 5 mM; and sodium pyruvate (BioSource International, Inc.) was added to 1 mM.

Burkitt's Lymphoma lymphoblastoid Namalwa cells (ATCC Accession No. CRL-1432) were grown by incubation in culture medium overnight. Cells were harvested by centrifugation in a tabletop centrifuge (1200 RPM for 5 minutes), and then resuspended in phosphate buffered sucrose to a concentration of 1.3×10^7 cells per milliliter.

For each transfection, a 750 µL aliquot of the cell suspension was placed in an electroporation cuvette with 4 mm gaps. 10 µg of the pIFN-α1-luc vector and 10 µg of the pCI-TLR6 vector were added to the electroporation cuvette. The cell and vector mixtures were incubated at room temperature for 5 minutes. The cells were electroporated using a BioRad Gene Pulser (BioRad Laboratories, Hercules, CA) set to at 500 µF capacitance and 0.27 volts, then incubated at room temperature for 5 minutes.

The electroporated cells were suspended in 10 mLs of culture medium and incubated overnight. Dead cells and debris were removed after 24 hours using a MACS

Dead Cell Removal kit (Miltenyi Biotec, Auburn, CA). Cells were resuspended in 10 mLs of culture medium and incubated for an additional 24 hours.

Transfected cells were selected by adding G418 (Promega Corp., Madison, WI) to a final concentration of 1 mg/mL and incubating the cells for seven days.

Assays

The selected transfected cells were counted and resuspended to a concentration of $1x10^6$ cell per mL in culture medium. 100 µl aliquots of cells were placed in the wells of a white-walled, white-bottomed 96-well plate (Corning, Inc. Corning, NY). 1.0 µL of an IRM compound from Table 1 (prepared at 1 mM in 100% DMSO) was added to some cell aliquots so that the final concentration of IRM compound was 10 µM. As a positive control, some cell aliquots were incubated with Sendai virus instead of IRM compound. As a negative control, some cell aliquots were incubated with DMSO without IRM compound. In all cases, the cells were incubated for 18 hours.

Table 1 - IRM Compounds

Compound	Chemical Name	Citation
IRM 1	4-amino-2-ethoxymethyl-α,α-dimethyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol	U.S. 5,352,784 Example 91
IRM 2	4-amino-α,α,2-trimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol	U.S. 5,266,575 Example C1
IRM 3	N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide	U.S. 6,331,539 Example 6
IRM 4	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine	WO 02/46193 Example 33
IRM 5	2-butyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 39
IRM 6	2-butyl-6,7,8,9-tetrahydro-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. 6,194,425 Example 40
IRM 7	N^3-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}-6-(1*H*-1-pyrrolyl)nicotinamide	U.S. 6,451,810 Example 60
IRM 8	2-ethyl-1-[5-(methylsulfonyl)pentyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine	WO 02/46192 Example 13

The plates were equilibrated to room temperature before 1 volume of reconstituted LucLight Plus (Packard Instruments, Meriden, CT) was added to each aliquot of cells. Each well of the plate was read on an LJL Analyst (LJL Biosystems, Inc., Sunnyvale, CA) set with a 5 minute dark adapt. Data from a representative experiment are shown in Table 2. The data are expressed as the fold increase in luciferase induction off of the IFN-α1 promoter in cell aliquots incubated with the indicated stimulant compared to the negative control in which the cell aliquots were incubated with only DMSO.

Table 2 - TLR Expression by pIFN-α1-luc/pCI-TLR6 Co-Transfected Namalwa cells

Stimulant	Fold Increase in Luciferase Induction
IRM1	3.6
IRM2	2.7
IRM3	2.6
IRM4	4.0
IRM5	3.2
IRM6	2.9
IRM7	3.2
IRM8	2.3
Sendai virus	2.7

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control.

Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is Claimed is:

1. An expression system comprising:

a first nucleic acid sequence that encodes a Toll-like receptor operably linked to a first expression control sequence; and

a second nucleic acid sequence that encodes a reporter that (a) generates a detectable signal when the reporter is expressed and the cell is exposed to conditions effective for generating the detectable signal, and (b) is operably linked to a second expression control sequence that comprises a cytokine promoter, a chemokine promoter, a co-stimulatory marker promoter, or a defensin promoter.

2. The expression system of claim 1 wherein the second expression control sequence comprises an IFN-α promoter.

3. The expression system of claim 1 wherein the first nucleic acid sequence comprises the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, or a degenerate variant of any of the foregoing.

4. The expression system of claim 1 wherein the first nucleic acid sequence comprises a nucleotide sequence that encodes a polypeptide having the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, or any one of the foregoing sequences with one or more conservative amino acid substitutions.

5. The expression system of claim 1 wherein the detectable signal comprises luciferase activity or β-galactosidase activity.

6. The expression system of claim 1 wherein a first vector comprises the first nucleic acid sequence and a second vector comprises the second nucleic acid sequence.

7. A vector comprising the expression system of claim 1.

8. A TLR agonist identified using the expression system of claim 1.

9. A pharmaceutical composition comprising the TLR agonist of claim 8, or a pharmaceutically acceptable salt thereof.

10. A cultured cell comprising the expression system of claim 1.

11. The cultured cell of claim 10 wherein the cell is a mammalian cell or a descendent of a mammalian cell.

12. The culture cell of claim 11 wherein the cell is a human cell or a descendent of a human cell.

13. The cultured cell of claim 10 further comprising an expressible nucleic acid sequence that encodes IFN-α operably linked to a third expression control sequence.

14. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN-α is located on a chromosome of the cultured cell.

15. The cultured cell of claim 14 wherein the cultured cell is a Namalwa cell.

16. The cultured cell of claim 13 wherein the expressible nucleic acid sequence that encodes IFN-α is located on an extrachromosomal vector.

17. A TLR agonist identified using the cultured cell of claim 10.

18. A pharmaceutical composition comprising the TLR agonist of claim 17, or a pharmaceutically acceptable salt thereof.

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Ghosh, Tarun K.
Fink, Jason R.

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Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp
        35                  40                  45

Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg
    50                  55                  60

Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu
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Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln
85 90 95

Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser
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Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu
115 120 125

His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val
130 135 140

Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser
145 150 155 160

Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu
165 170 175

Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp
180 185 190

Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln
195 200 205

Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe
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Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys
225 230 235 240

Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser
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Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys
260 265 270

Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val
275 280 285

Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe
290 295 300

Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly
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Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln

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Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln
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Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro
    355                 360                 365

Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu
    370                 375                 380

Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr
385                 390                 395                 400

Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys
            405                 410                 415

Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His
        420                 425                 430

Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr
    435                 440                 445

Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser
    450                 455                 460

Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro
465                 470                 475                 480

Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp
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Ser Ser Pro Ser Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp
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Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly
    515                 520                 525

Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg
    530                 535                 540

Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly
545                 550                 555                 560

Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu
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Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn
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Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser
610 615 620

Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu
625 630 635 640

Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp
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Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser
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Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val
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Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu
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Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val
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Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp
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Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu
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Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu
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Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
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Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
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His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile
835 840 845

Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
850 855 860

Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
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Leu Gly Ser Lys Asn Ser Val His
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Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
35 40 45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
50 55 60

Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
65 70 75 80

Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr
85 90 95

Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu
100 105 110

Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro
115 120 125

Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser
130 135 140

Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln
145 150 155 160

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
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Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
180 185 190

Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
195 200 205

Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
210 215 220

Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
225 230 235 240

Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
245 250 255

Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
260 265 270

Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
275 280 285

Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
290 295 300

Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
305 310 315 320

Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
325 330 335

Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
340 345 350

Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe

355 360 365

Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu
370 375 380

Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
385 390 395 400

Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
405 410 415

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
420 425 430

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
435 440 445

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
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Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
465 470 475 480

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
485 490 495

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
500 505 510

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
515 520 525

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
530 535 540

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
545 550 555 560

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
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Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
580 585 590

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
595 600 605

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Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
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Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
                645                 650                 655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
            660                 665                 670

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
        675                 680                 685

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
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Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu
705                 710                 715                 720

Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
                725                 730                 735

Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
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Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
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Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
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aactccaaca ggctgacagt tctttctcac aatgatttac ctgctaattt agagatcctg     180

gacatatcca ggaaccagct cctagctcct aatcctgatg tatttgtatc acttagtgtc     240

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35 40 45

Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln
50 55 60

Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe
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Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly
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Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp
        115                 120                 125

Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr
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Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln
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Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His
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Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
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Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
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Lys Arg Gly Leu Phe Trp Ala Asn Ile Arg Ala Ala Phe Asn Met Lys
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Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
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Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
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Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
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Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
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Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
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Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
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Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu
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Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
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Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
    50                  55                  60


Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
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Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
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Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
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Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
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Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
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Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
180 185 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
195 200 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
210 215 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225 230 235 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
245 250 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
260 265 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
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Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
290 295 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305 310 315 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
325 330 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
340 345 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
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Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
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Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
385 390 395 400

Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
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Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
420 425 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
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Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
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Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
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Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
485 490 495

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515 520 525

Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
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Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
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Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
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Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
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His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
595 600 605

Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
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Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
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Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn

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Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
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Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
675 680 685

Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr
690 695 700

Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
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725 730 735

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
740 745 750

Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
755 760 765

Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
770 775 780

Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
785 790 795 800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
805 810 815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe
820 825 830

Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
835 840 845

His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
850 855 860

Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
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Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
885 890 895

Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
900 905 910

Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
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Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
930 935 940

Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
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Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
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Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
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Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
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Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
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Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
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Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
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Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
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Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
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Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
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Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
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His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
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Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
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Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
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Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
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Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
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Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
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Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn

595 600 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
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Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
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His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
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Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
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Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
675 680 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
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Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
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785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
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Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
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Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
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Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
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35 40 45

Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln
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Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys
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Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr

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Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr
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Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys
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Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg
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Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly
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His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu
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Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr
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His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn
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Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys
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Glu Leu Lys Asn Phe Ile Gln Leu Glu Thr Tyr Ser Glu Val Met Met
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Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg
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Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr
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Ala Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu
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Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu
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Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe
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Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys
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Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu
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Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu
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Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr
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Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys
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Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp
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Ala Asn Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu
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